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(54) Sterilizing cyanoacrylate preparations

(57) Cyanoacrylate preparations for medical and surgical adhesive applications are sterilised by heating in a suitable container at a temperature of at least 160°C. The preferred container is a squeezable aluminium tube and the preferred temperature is above 170°C. Cyanoacrylate adhesive compositions sterilised by heat have improved shelf life compared to those sterilised by ionising radiation.

GB 2 306 469 A

ADHESIVE COMPOSITION

The present invention relates to cyanoacrylate preparations and, more particularly, to the sterilisation of cyanoacrylate preparations for use in medical or surgical procedures and to sterilised cyanoacrylate packages.

It is known to use 2-cyanoacrylate esters for bonding tissue in medical or surgical procedures performed upon the human or animal body. 2-cyanoacrylate esters polymerise rapidly, and often instantaneously, upon contact with tissue or fluid. The cyanoacrylate polymer is thereafter degraded, metabolised and removed from the body.

In order to be used for medical, including surgical, purposes, 2-cyanoacrylate ester preparations must be sterilised.

It is known to sterilise 2-cyanoacrylate preparations by the use of heat or of radiation. Both techniques tend to cause polymerisation of the cyanoacrylate monomer, or at least tend to reduce the shelf life. There therefore remains a demand in the market place for sterilised 2-cyanoacrylate adhesive compositions which have a good shelf life.

It is believed that sterile 2-cyanoacrylate preparations now on the market have, in the main, been sterilised by the use of ionising radiation. Whilst ionising radiation has, therefore, apparently been perceived as the preferred method of sterilisation, there is a substantial capital cost associated with this procedure and it necessitates the careful use of dosimetry procedures. The biological effects of radiation can also create their own problems.

Cyanoacrylate monomer must be packaged in an inert and adequately water-resistant container, since atmospheric moisture causes polymerisation. Aluminium containers, and more particularly tubes, are sometimes used for cyanoacrylate sold for industrial or

commercial purposes.

Polyolefin has been the material of choice for commercial medical-grade cyanoacrylate. Polyolefin containers however are permeable to atmospheric moisture the ingress of which into the container detrimentally affects the properties and shelf life of the stored cyanoacrylate. As already stated, both heat and ionising radiation tend to cause or promote polymerisation of 2-cyanoacrylate monomer, at least to the extend of reducing shelf life and, accordingly, sterile cyanoacrylate requires a container which will not promote or cause polymerisation during the sterilisation process. Aluminium has not found favour as a container for sterile cyanoacrylate.

The present invention provides a novel method of sterilising a 2-cyanoacrylate ester preparation. The method contradicts known teaching as to the stability of cyanoacrylate and yet enables production of a product of outstanding stability. The invention also provides a novel sterile 2-cyanoacrylate ester preparation and a novel package containing sterile cyanoacrylate.

The Method

In one aspect the invention provides a method of sterilising a 2-cyanoacrylate ester preparations, comprising heating the preparation to a temperature of at least 160°C. The prior art teaches that cyanoacrylate polymerises at a temperature of 160°C (US Patent No. 3360124). The sterilisation method is preferably formed at a temperature of at least 170°C and more preferably at a temperature of about 180°C, or more.

The British Pharmacopoeia recommends heating at a minimum of 160°C for not less than 2 hours, a minimum of 170°C for not less than 1 hour and a minimum of 180°C for not less than 30 minutes for effective sterilisation. In accordance with the present invention, the 2-cyanoacrylate ester preparations are preferably heated for a period of time in accordance with

the recommendations of the British Pharmacopoeia. It is most preferred that the cyanoacrylate preparation is maintained at a temperature of about 180 °C for at least 30 minutes, and more preferably for about 45 minutes. Such processes have, against all expectations, been found capable of resulting in a product which not only equals the stability of prior art sterile cyanoacrylate preparations but exceeds the stability of such preparations by a considerable margin.

Thus it has surprisingly been found that when the method of the invention is performed upon 2-cyanoacrylate ester preparations contained in an aluminium container, it is possible for the sterilised cyanoacrylate to retain its fluidity for a period in excess of 220 days at 55°C.

This compares with fluidity retention periods at 55°C of 4 days and 6 days for two sterile cyanoacrylate products on the market. The method of the invention is therefore preferably performed upon a sealed aluminium container, although alternative thermally stable containers may be used. A particularly preferred container is an aluminium tube, e.g. a tightly crimped aluminium tube.

The method of the invention is not restricted as to the method of heating but dry heat sterilisation is preferred. In an exemplary procedure, closed containers of cyanoacrylate preparation are placed in a dry heat steriliser pre-heated to 180°C. The steriliser temperature is allowed to return to 180°C and the containers are held in the steriliser for a period of at least 30 minutes and more normally of up to 45 minutes.

The Preparation

The method of the invention may be applied in principle to any 2-cyanoacrylate ester. The cyanoacrylate is preferably an aliphatic 2-cyanoacrylate ester and preferably an alkyl, cycloalkyl, alkenyl or alkoxyalkyl 2-cyanoacrylate ester. The alkyl group may have from 1 to 16 carbon atoms and is more preferably a C_1-C_8 alkyl ester and most preferably a C_1-C_4 alkyl

ester. Suitable esters include the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pentyl, heryl, cycloheryl, heptyl, octyl, 2-methoxyethyl and 2-ethoxyethyl esters of cyanoacrylic acid.

The cyanoacrylate preparation will contain any additives necessary to impart the desired properties to the preparation as viscosity, colour, X-ray opacity, etc. Commercial medical cyanoacrylate preparations contain one or more additives to prevent premature polymerisation. Usually, cyanoacrylate monomers are stabilised with anionic and free-radical polymerisation inhibitors. Anionic polymerisation inhibitors known in the art include soluble acidic gasses (for example sulfur dioxide), and phosphoric, carboxylic and organic sulphonic acids. Free-radical polymerisation inhibitors include hydroquinone, t-butyl catechol, hydroxyanisole, butylated hydroxyanisole and butylated hydroxytoluene.

The Package

The heat-sterilised cyanoacrylate preparations of the invention may be packaged in a container made of any suitable material. In this respect, the container must be heat-resistant up to the sterilisation temperature, present an adequate barrier to atmospheric moisture and he cyanoacrylate-compatible. Materials meeting these requirements include metal and glass. A particularly preferred material is aluminium, especially aluminium formed into a squeezable tube. Preferred aluminium tubes comprise a nozzle which is hermetically sealed by a pierceable membrane of aluminium and are filled at their end remote from the nozzle prior to closure of the open end by tight crimping. In the result, therefore, preferred embodiments of the invention reside in a substantially hermetically sealed aluminium container, e.g. an aluminium tube, containing a sterile 2-cyanoacrylate ester preparation.

The present invention enables provision of 2-cyanoacrylate ester preparations which retain their fluidity at 55℃ for a prolonged period when in a sealed aluminium container. Preferred preparations are capable of retaining their fluidity at 55℃ for a period of at least 50 days when in a sealed aluminium container, and more preferably for a period of at least 100 days.

Particularly preferred preparations are capable of retaining their fluidity at 55 C for a period of at least 200 days, e.g. 220 days or more. As measured in this way, the invention enables provision of sterile adhesive having a stability in excess of 36 times that of two products currently on the market.

The invention is further illustrated in the following example

Example

A preparation was made of n-butyl 2-cyanoacrylate (NBCA) stabilised with 100 ppm SO_2 and 1000 ppm butylated hydroxyanisole. The preparation was placed into aluminium tubes and sterilised by ionising radiation (γ and electron beam radiation) and by heating. The stabilities of the resultant products were compared with each other and with the stabilities of two commercially available medical grade cyanoacrylates. The ability of the preparations to polymerise promptly upon application to tissue was checked by ascertaining polymerisation time on bovine plasma.

1. Sterilisation procedures:

NBCA was filled into aluminium tubes, which were hermetically closed by tight crimping.

a. Dry heat sterilisation: The tubes are placed in a preheated, validated dry heat steriliser. The tubes are kept for 45 minutes once the temperature levels at 180°C. (The theoretical sterilisation time at this temperature is 9 minutes. The recommended sterilisation cycle in British Pharmacopoeia (p.A197, Vol II, Ed. 1993) is 30 minutes at 180°C.)

b. Ionising radiation: The tubes were placed in validated ionisation chambers where they received the prescribed dose of 25 kGy (British Pharmacopoeia, p.A198, Vol II, Ed. 1993) of γ or e^- beam exposure.

2. Polymerisation time on bovine plasma:

Freshly reconstituted bovine plasma in a suitable container is placed and equilibrated in a

water bath at 37°C. Using a 27 Gauge needle a drop of NBCA is dropped on the plasma surface from a distance of 2 cm. The time interval from the moment the drop hits the surface to the moment it polymerises (looses transparency) is measured with a stopwatch.

3. Stability at 55°C:

Aluminium tubes containing NBCA prior to and following sterilisation are placed at a constant temperature of 55°C and monitored daily for fluidity of the cyanoacrylate by shaking. The number of days with retained fluidity is recorded. This is a widely practiced accelerated stability test for cyanoacrylate adhesives relating to their shelf-life.

The results are shown in Tables 1 and 2 below.

Table 1

Properties of NBCA following different sterilisation treatments

No	Sterilisation method	Sterilisation details	Polymerisation time on bovine plasma	Colour	Viscosity increase after sterili-sation	Stability at 55°C (days)
1	none	-	instant	APHA 100	-	>220
2	γ	25 kGy	instant	Gardner 5	yes	12
3	e⁻ beam	25 kGy	instant	APHA 300	yes	36
4	dry heat	45 min at 180°C	instant	APHA 200	no	>220

Table 2

Comparison of properties of NBCA medical adhesives

NBCA	Sterilisation method	Polymerisation time on bovine plasma	Appearance	Stability at 55°C (days)
Competitor No 1	unknown	instant	intentionally coloured blue	4
Competitor No 2	γ-radiation	2 seconds	clear, APHA 100	6
Product # 4 of Table 1	dry heat	instant	clear, APHA 200	>220

CLAIMS:

1. A method of sterilising a 2-cyanoacrylate ester preparation, comprising heating the preparation to a temperature of at least 160°C.

2. A method of claim 1, wherein the preparation is heated to a temperature of at least 170°C.

3. A method of claim 2, wherein the preparation is heated to a temperature of about 180°C.

4. A method of claim 3, wherein the preparation is maintained at a temperature of about 180°C for at least 30 minutes.

5. A method of claim 4, wherein the preparation is maintained at a temperature of about 180°C for about 45 minutes.

6. A method of any of claims 1 to 5, wherein the preparation is contained in an aluminium container during performance of said heating.

7. A method of any of claims 1 to 6 wherein the preparation is an alkyl, cycloalkyl, alkenyl or alkoxyalkyl 2-cyanoacrylate preparation.

8. A method of claim 7, wherein the preparation is a C_1-C_4 alkyl 2-cyanoacrylate preparation.

9. A method of claim 8, wherein the preparation is n-butyl 2-cyanoacrylate preparation.

10. A method of any of claims 1 to 9, wherein the 2-cyanoacrylate ester preparation contains sulphur dioxide and butylated hydroxyanisole as stabilisers.

11. A package comprising a sealed aluminium container containing a sterile 2-cyanoacrylate

ester preparation.

12. A package of claim 11, wherein the 2-cyanoacrylate preparation retains its fluidity at 55 ℃ for a period of at least 50 days.

13. A package of claim 12, wherein the 2-cyanoacrylate ester preparation retains its fluidity at 55℃ for a period of at least 200 days.

14. A package of any of claims 11 to 13, wherein the 2-cyanoacrylate ester preparation is defined in any of claims 7 to 10.

15. A package comprising a sealed container containing sterile 2-cyanoacrylate ester preparation, the preparation being capable of retaining its fluidity at 55 ℃ for a period of at least 50 days when in a sealed aluminium container (e.g. an aluminium tube).

16. A package of claim 15, wherein the preparation is thus capable of retaining its fluidity at 55℃ for a period of at least 200 days.

17. A package of claim 15 or claim 16, wherein the preparation is as further defined in any of claims 7 to 10.

18. A sterile 2-cyanoacrylate ester preparation for use in medicine or surgery, the preparation being contained in a sealed aluminium container and optionally as defined in any of claims 12 to 14.

19. A sterile 2-cyanoacrylate ester preparation for use in medicine or surgery, the preparation being in a sealed container and being capable of retaining its fluidity at 55℃ for a period of at least 50 days when in a sealed aluminium container, and optionally being as defined in claim 16 or claim 17.

20. A method of bonding human or animal tissue, comprising applying to the tissue a preparation as defined in claim 18 or claim 19.